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13. ABSTRACT (Maximum 200 words) Using our novel animal models of severe hemorrhage, focusing on evaluation of outcome to 3-10 days, the following strategies were found superior in terms of intact survival compared to standard resuscitation. Project I on hemorrhagic shock revealed benefit from limited (hypotensive) titrated fluid resuscitation; mild hypothermia during shock and resuscitation; additional use of antioxidant tempol i.v. or intraperitoneal; titrated i.v. administration (instead of bolus) of hypertonic/hyperoncotic solution for preventing cardiac arrest during uncontrolled hemorrhagic shock; and peritoneal oxygenation and medication. Program II on "suspended animation" was in novel animal models of severe hemorrhage to cardiac arrest (no blood flow), the prevalent cause of death in combat. Hypothermic strategies with cold saline flushed into the aorta within the first 5 minutes of cardiac arrest was found to be most effective in preserving the organism for up to 1-2 hours of clinical death. Resuscitation must be with artificial circulation (emergency, portable heart-lung machine). Using small flush volumes plus drugs, the testing of 14 different pharmacologic strategies revealed disappointing results. Special cold preservation solutions tested revealed only minor advantage over cold saline. Industries are being advised for the development of rapid vessel access methods ("smart catheter") and of hypothermia induction with blood cooling in the field.				
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FINAL REPORT

GRANT NO: N000-97-1-1064, N000-98-2-1064, and N000-14-99-1-0765

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GRANT TITLE: NOVEL RESUSCITATION FROM LETHAL HEMORRHAGE.
Increasing survival of combat casualties.
Project I: Hemorrhagic shock (HS) in rats. Tisherman et al
Project II: Suspended animation (SA) in dogs. Safar et al

AWARD PERIOD: 1 Oct 1997 – 31 July 2001

OBJECTIVE: To help maximize the reversibility of presently lethal traumatic hemorrhage. In *project I* on hemorrhagic shock (HS) (low blood flow) in rats, to extend beyond the "golden hour" of HS tolerance – the prevalent cause of soldiers having "died of wounds" (DOW) -- by preventing cardiac arrest (CA) during HS and multiple organ failure (MOF) after resuscitation. In *project II* on rapid exsanguination to CA (no blood flow), in dogs -- the prevalent cause of soldiers killed in action (KIA) -- to develop a totally new approach for this presently unresuscitable condition (and unresuscitable CA in civilian EMS). We term this method "suspended animation (SA) for delayed resuscitation," i.e., preservation of brain and organism during clinical death of 1-2 h, to buy time for transport, surgical hemostasis, and initiation of resuscitative cardiopulmonary bypass (CPB). Support of projects I and II was initiated by U.S. Navy Commander Lyn Yaffe, project II on SA inspired by U.S. Army surgeon Ronald Bellamy. Our HS and SA projects were designed to systematically explore, in the first 5 years, the most promising pharmacologic and hypothermic strategies to maximally increase the tolerance of these insults in terms of outcome, i.e., survival without brain damage. We specifically explored mild hypothermia (Hth) (33-36°C) or moderate Hth (28-32°C) for HS (spontaneous circulation) and deep Hth (16-27°C) and profound Hth (5-15°C) for CA. Our results should guide future development of devices and techniques for initiation in the field. Both HS and SA studies have been for *preservation* [treatment during the insult], followed by *resuscitation* [treatment to reverse the insult]. The efficacy of mild Hth after normothermic CA, first documented by us in dogs, has now also been documented in patients (see *NEJM*, early 2002 in press, with our editorial).

APPROACH: For *project I* on HS, we used our established unique outcome models in rats, with targeted modifications in selected studies (2,3). We used uncontrolled HS (tail amputation), pressure-controlled HS, or volume-controlled HS. HS was initiated with bleeding 3 ml/100 g over 15 min. HS phase 1 of 60-180 min with mean arterial pressure (MAP) prevented from dropping below 40 mm Hg; and resuscitation phase 2 of 1-3 h for hemostasis and all-out i.v. fluid resuscitation (FR) with return of initially shed blood plus lactated Ringer's solution (LR) are followed by observation phase 3 of 72 h (range 24 h - 10 days). Principle endpoints were survival time and survival rate to 24 h or 72 h. We used established outcome measurements of overall, neurologic, and cognitive function, and morphology. We also explored some mechanisms related to treatments studied. Phases 1 and 2 were with standardized light inhalation anesthesia and spontaneous breathing via mask; phase 3 was without anesthesia. During phases 1 and 2 we monitored visceral dysoxia as increased PCO₂ on the surface of liver and gut (7-9). During phase 3 we monitored heart rate and activity, and controlled core temperature (T) using a radio transmitter in the abdomen (7-9). We explored therapeutic hypothermia (1,4,10,17,18,45), hyperoxia (increased FiO₂) (7-9), novel drugs and fluids (15,16), and peritoneal strategies (13,39,43).

For *project II* on SA, we used modifications (60) of our unique CA outcome models in custom-bred hunting dogs of 20-25 kg weight (50-64). Normothermic exsanguination over 5 min led to CA no flow for periods ranging between 15 min and 120 min – CA at various temperatures (57,60,61). Preservation was induced within the first 5 min of CA by flushing isotonic NaCl (saline) into the aorta via a balloon catheter, with or without special drugs or fluids added. On drugs, during years 1 and 2, we received input from neuroscience subcontractors Drs. Hayes, Sick, Siesjo, and Bickler. At the end of CA, resuscitation was with closed-chest (emergency) cardiopulmonary bypass (CPB), restoration of spontaneous circulation (ROSC),

prolonged controlled ventilation for at least 24 h, weaning, and intensive care to at least 72 h. We measured outcome as overall performance categories (OCP) 1-5 (OCP 1 = normal, 2 = moderate disability, 3 = severe disability, 4 = coma, 5 = death); neurologic deficit scores (NDS) 0-100% (NDS 0-10% normal, 100% brain death); and after euthanasia, brain histologic (light microscopic) damage scores (HDS) and extracerebral organ systems morphology. We explored a new method of testing cognitive function in dogs (58,61) (Dr. Dixon).

ACCOMPLISHMENTS: During this reporting period of 46 months, project I on HS used 1,436 rats and project II on SA used 290 dogs. In both projects, pilot experiments led to exploratory mini-series, which led to definitive randomized outcome studies. The results of each study led to hypotheses and questions for the next study. Guided by P.I. (Dr. Safar) and Co-P.I. (Dr. Tisherman), critical care medicine (CCM) physician research fellows (Drs. Takasu, Woods, Carrillo, Barr, Wu, Kentner, Prueckner, Behringer) were project team leaders. These physicians were helped by 3-6 lab technicians (coordinated by Mr. William Stezoski) and influenced by over 10 co-investigators and consultants. Weekly lab meetings and annual outside investigators' meetings influenced plans, protocols, and results.

Accomplishments of Project I on HS in Rats. Around 1990 we had discovered a significant increase in survival time in conscious rats with lethal volume-controlled HS with moderate Hth by surface cooling as compared to normothermia (37-38°C), or under normothermia by increasing FiO_2 from 0.21 to 1.0 (5-9) (hyperoxia). We used hitherto unpublished data of our past experiments in awake rats to analyze and now report that volume HS of 180 min (lethal with normothermia) can be survived by combining moderate Hth plus FiO_2 1.0 during HS (4). In the early 1990s we developed a clinically more realistic uncontrolled HS outcome model -- with tail amputation (2,3). For pain and steady-state control we used standardized light general anesthesia and spontaneous breathing. During uncontrolled HS, limited (hypotensive) FR (MAP 40 mm Hg) with LR, had survival benefit over normotensive or no FR (2,3). Additional *mild hypothermia* (Hth) by surface cooling, during uncontrolled HS and FR, increased survival time and 72 h survival rate (5-10). This was a "first." Even when Hth was delayed until FR (phase 2), did it increase survival time (19). Mild Hth was as effective as moderate Hth. There was no gross shivering when conscious rats were kept under mild Hth (35°C) during phase 3. *Hyperoxia* with FiO_2 1.0 did not significantly increase survival time or rate (9). FiO_2 0.5, however, had some survival benefit (NS) when added to mild Hth. FiO_2 1.0 during uncontrolled HS and FR supported MAP without increasing bleeding. Hth or hyperoxia transiently mitigated visceral dysoxia during HS. Mild Hth (Tr 34°C) supported MAP during HS in the uncontrolled HS model (5), but when tested in the pressure-controlled (MAP 40 mm Hg) HS model, survival benefit from Hth was retained (10). Therefore, Hth benefit does not depend on the ability of Hth to increase MAP (10). In general, non-survivors (irrespective of temperature) that died on days 2 or 3 had developed gut necrosis. Survivors to 72 h showed grossly normal function and grossly morphologically normal organs.

Mechanism studies were added (10,12,16,17,20). We postulated that the most vulnerable organs after HS are the viscera, while the brain protects itself by vasodilation. Using a pressure-controlled HS outcome model with MAP 30-40 mm Hg for 45-60 min at normothermia, we found normal cognitive function values at 10 days, as well as normal brain histology, normal neuron cell counts, and no neuronal DNA damage (11,21). Rats with poor outcome had apoptotic and necrotic lesions in liver and small intestine (28). Antioxidant reserve in plasma and (more so) in the liver, was reduced to a lesser degree at the end of HS and FR in rats treated with mild Hth compared to normothermic controls (25) (Dr. Kagan). Plasma levels of IL-1 β and IL-6 were lower and those of IL-10 and TNF- α were higher during HS, using mild Hth compared to normothermia (17,20). The increase in survival rate achieved with mild Hth during HS could not be achieved by isolated cooling of the gut -- rather it required cooling of the whole organism (18). Recently we found in pigs with liver trauma that mild Hth during HS and FR may not cause coagulopathy (49).

Resuscitation fluids and drugs were explored, i.e., outcome compared to that with use of LR, using mostly the uncontrolled HS model. In our previous studies, colloid or whole blood had proved superior to LR. In our uncontrolled HS model, polynitroxylated albumin (PNA) plus *tempol* (a water-soluble antioxidant) increased survival compared to albumin (16). Tempol was effective when given early during HS (38), but not when given late (37). We explored hypertonic/hyperoncotic solution (HHS) we explored with a novel mode of administration, namely *titration*, instead of the previously studied bolus administration (15); titrating HHS to maintain MAP at ≥ 40 mm Hg during HS of 2 h did not increase survival rate, but did not cause increased bleeding and achieved the same survival with only one-tenth of the fluid volume required with use of LR (15).

Ringer's ethylpyruvate (an antioxidant) solution did not improve survival time and rate compared to LR (47), nor did amelioride as Na⁺/H⁺ exchange inhibitor (48). Oral or enteral IL-6 during HS was not beneficial (12). We explored intra-peritoneal strategies to preserve the viscera during HS. *Intraperitoneal ventilation* with oxygen or air increased survival time and rate (13). Intraperitoneal (but not enteral) adenosine improved survival (14). In the last study, using lethal uncontrolled HS of 2 h (MAP \geq 40 mm Hg) an optimized *combination treatment* during HS phase 1 was most effective (45): compared with control group 1 under normothermia with LR, mild Hth during HS (group 2) increased survival; but mild Hth plus PNA-tempol during HS (group 3) increased survival further. All of the above plus peritoneal adenosine (group 4) gave worse survival data (perhaps because of the added trauma, laparotomy).

Accomplishments of Project II on SA in Dogs. In normothermic CA with \geq 15 min no flow or CA in profound Hth, external CPR is ineffective and CPB is needed to achieve ROSC. In years 1-2, we modified our past SA model (50,51) which used CPB for induction of preservation (SA) at the start of CA with profound Hth. In the modification, the induction of SA was with a single flush of cold saline via an aortic balloon catheter (53). This method is likely to be more feasible than CPB in the field or in field hospitals. For that we are advising industries to work on novel vessel-access methods – insertion of an aortic balloon catheter percutaneously, through cutdown or via thoracotomy (Dr. Klain, Dr. Yaffe, Cardeon Co.); and for a miniaturized cooling/pumping device. In our dog outcome studies (see "approach") the aortic balloon catheter was placed in the upper thoracic aorta to first rapidly preserve brain and heart. Starting at CA 2 min normothermic no flow, normothermic flush of 500 ml at 37.5°C over 1 min did not improve outcome (53,65); however, the same with saline at 24°C achieved brain (tympanic membrane) temperature (Tty) 36°C; and saline flush at 4°C achieved Tty 34°C, all within 1-3 min flush (53). Flush with 24°C saline at start of CA 15 min no-flow achieved functional normality at 72 h, but *with* histologic damage (53). Flush with 4°C saline (Tty 34°C) at start of CA 15 min achieved functional and histologic normality (53). Catheter design influenced outcome; with the opening at the tip, the straight flush resulted in better outcome than using a catheter with the tip closed and the flush through multiple lateral openings. For adding drugs with preservation potential, the control protocol had to achieve, at 72 h, survival *with* brain damage in all dogs. That was CA 20 min no flow and flush at the start of CA with saline at room temperature (24°C) (54).

In years 2-3, we were searching for a breakthrough effect among 14 different *drugs* added to the saline flush, and in some cases also to the reperfusion fluid. For individual dogs' and drugs' results see table in reference (59). The drugs were selected according to one or more of six mechanistic strategies, documented by us and others in the past: 1) delaying energy failure; 2) combating depolarization of membranes; 3) inhibiting proteases; 4) inhibiting apoptosis; 5) inhibiting reoxygenation injury; and 6) protecting mitochondria. The drugs were selected on the basis of published results in rodents and advice from our co-investigators and consultants. Subcontractors supplied their own published and new data. Most drugs tested had not yet been evaluated for outcome after prolonged CA in large animals. We were seeking a breakthrough effect, namely OPC = 1 at 72 h in 2-3 dogs of exploratory mini series of 3-6 experiments each. OPC = 1 was achieved in very few cases (59). Adenosine did not abolish the previously seen histologic damage after CA 15 min (55). In the CA 20 min Tty 36°C model, when thiopental, thiopental plus phenytoin, or insulin plus glucose was added to flush and reperfusion, only 3/20 dogs achieved OPC 1, while 17 achieved only OPC 3 or 4 (severe damage) (56). Even in dogs with OPC 1, none of the brains were histologically normal (total HDS 0-30). HDS were always severe and correlated with NDS. With CA 20 min, flush with the antioxidant *tempol* resulted in OPC 1 or 2 (good outcome) in all 8 dogs (58). Tempol was also effective with CA 40 min, and 50 ml/kg flush at 4°C, to Tty 28°C (58). In both it improved function, but did not significantly improve brain HDS (58). An explanation for this is speculative. These antioxidant experiments also searched for mechanisms (58). Treatment with any of 11 other drugs resulted only in dogs achieving OPC 3 or 4, severe NDS and severe HDS (55-59). Thus, in this unique systematic exploration in 84 dogs, only tempol looked promising. Either tempol or other brain penetrating antioxidants should be pursued further.

In years 3-4, we used the same model for exploring *hypothermic strategies* without drugs. We systematically extended the CA (no flow) period from 20 min (54), to 30 min (60), and to 60-120 min (61,62). The lower the Tty after flush the better was preservation for increasing CA duration. Saline at 4°C flushed with a 1L/min flow rate, decreased Tty by 3°C/min. This is more rapid than with any other cooling method except CPB. With CA 20 min no flow (54) aortic arch flush rapidly lowered Tty to 34°C, and achieved survival to 72

h with functionally normal and histologically minimal damage. A delay in flush during normothermic CA to 8 min no flow before start of cold flush negated the preservation achieved with flush starting at CA 2 min or 5 min (84). When we increased CA to 30 min no flow (60), we found that the flush volume of saline at 4°C had to be increased to 100 ml/kg to achieve functionally normal brains, and in some dogs even histologically normal brains; the aortic balloon had to be inflated in the abdominal aorta to also protect the viscera and spinal cord against ischemic damage (60,61,62). For flush preservation in adult humans (70 kg), this translates to 7L of iced saline. Aortic flush to Tty 20°C, 15°C, or 10°C preserved the brain and organism long enough to achieve intact survival (OPC 1) after 60 min, 90 min, and in some dogs even 120 min no flow (61). All 6 dogs with CA 90 min and Tty 10°C were functionally normal. One dog after CA 90 min, one after CA 60 min, and one normal dog received cognitive function tests months later; these were normal. Functional and histologic studies of extracerebral organs after 72 h have been initiated (86). CA up to 60 min was survived with intact viscera, with liver malfunction only transient (75). In the last study, with CA 120 min, when flush was with Normosol, Unisol, and tempol *combined*, all six dogs achieved good outcome (OPC 1 or 2) (62). We found only minimal outcome benefit from using solutions other than saline for the cold flush, stasis, and reperfusion. Using the CA 30 min model (83), outcome after use of albumin 5% or 20% was not different than with saline. PNA-tempol (Synzyme Co.) gave slightly better NDS than saline. A novel cerebral and cardiac preservation solution designed by our consultant Dr. Taylor (Unisol, extra- and intracellular, Organ Recovery Systems Co.) resulted in easier restoration of stable spontaneous circulation, but no improvement in OPC and NDS (83). We communicated with Dr. Rhee (ONR-USUHS), who was inspired by our work, and who researched SA with asanguinous *low flow* (not CA), using CPB via thoracotomy in pigs. This adds to our current (year 4) SA trauma studies in preparation for clinical trials.

Other accomplishments. For the rapid induction of mild Hth under spontaneous circulation (after CA, during HS, or other indications), blood cooling proved preferable to surface cooling. We found veno-venous pumping of about 10% cardiac output flow via a cooler to decrease Tty in dogs to the target level of 34°C in about 6 min (M34). Drs. Safar, Tisherman, Behringer, and alumni of this ONR project contributed to the revisions of Emergency Cardiac Care Guidelines 2000 by the American Heart Association in 2000. The P.I., Co-P.I., and fellows, throughout, presented an average of one lecture per month on a variety of topics, including those related to the HS and SA projects. In 2000, the P.I. presented 10 invited, named lectures outside. In 1999, SCRR Director Dr. Patrick Kochanek, conducted the 20-year anniversary program, which included honoring of and gratitude for the ONR. Subcontractor Dr. Siesjo presented the University of Pittsburgh's annual Safar Lecture of 1999. We co-initiated and helped the NIH PULSE initiative intended to boost coordinated support of resuscitation research, including traumatology, which was particularly supported by our group. Dr. Tisherman was co-chairman of the CNS panel. Dr. Safar was asked to give input for all NIH panels. Our group led new initiatives at local, national, and international levels for boosting the weakest link in civilian EMS, life-supporting first aid (LSFA) skill acquisition by the public (M8). Three fellows received awards at meetings for our ONR work. ONR held an animal models meeting where our group summarized 15 different models of shock or CA, developed and used since the 1960s. In 1999, we co-conducted in Baltimore, with the Shock Trauma Center, a planning session for clinical trials. On honors and awards, the P.I. gave the invited Wright Memorial Lecture of the American Society of Anesthesiologists on "Resuscitation Medicine in 1000 - 2000 C.E." The P.I. received his fourth elected honorary membership of Academies of (Medical) Sciences, i.e., that of Russia. The Co-P.I. gave talks related to our ONR research for the American Society of Artificial Internal Organs, the Japanese Reanimatology Society 2000, the Shock Society Meeting, and the International Surgical Society (on Fluid Resuscitation). The Co-P.I. received the Shubin-Weil Award of the Society for Critical Care Medicine. The P.I. coached a Ph.D. student on CA-CPCR related research: 1) Earliest possible prediction of futility in comatose survivors of CA (M29); 2) Hypertensive reperfusion from prolonged CA in patients correlates with good cerebral outcome (M28).

CONCLUSIONS: Preservation of the organism during HS (low flow) or CA (no flow) with hypothermic strategies is more effective than with pharmacologic strategies. In clinically relevant rat outcome models of HS, the benefit of mild Hth and of low-volume (hypotensive) FR is reproducible. For life support during uncontrolled HS, titrated hypotensive FR with a hypertonic/hyperoncotic solution and the antioxidant tempol are promising therapies, without risk of rebleeding. Antioxidants may be more effective when given at the beginning of HS or CA than during reperfusion. For severe, prolonged HS, peritoneal strategies should be pursued further for oxygenating, medicating, and cooling. For presently unresuscitable exsanguination CA, buying time beyond the normothermic CA tolerance limit of 5 min is possible with hypothermic strategies:

With Tty 10°C (induced with saline 4°C flush starting at CA 2 min) one can count on full preservation of all organs' viability after up to 90 min no flow. On SA, *we are on schedule* with our initial estimate that it will require about 5 years for pathophysiologic work to clarify limits and potentials (1997-2002) and another 5 years for development of devices and methods and initiation of transfer to patients.

SIGNIFICANCE: Concerning HS (low flow, spontaneous circulation), our documentation in rats of survival benefit from *mild hypothermia* (34°C), during HS, without causing increased bleeding is a "first." This has considerable clinical potential. How long to sustain Hth during and after FR remains to be determined. The doctrine for first aid of "keep him warm" may have to be changed. Since mild hypothermia is simple to induce and safe, and moderate hypothermia (30°C) as well as hyperthermia are risky, first aid should include temperature control. If trauma more extensive than tail amputation is added, Hth-induced coagulopathy may play an important role. At 34°C, this does not seem to be the case, as in our year-4 study conducted in pigs (also under ONR support). The fact that in rats with healthy lungs, breathing O₂ 100% does not improve outcome, is good news for military strategists concerned with supplies via air. The antioxidant *tempol*, alone or with colloid (PNA, Synzyme Co.) with outcome benefit in our rat model, should be pursued for FDA approval. The use of small-volume, *titrated* HHS has significance in the combat situation, in which the volume of available fluid is limited and prevention of CA during very long HS is difficult. The doubling or tripling of the "golden hour" by Hth plus other strategies (antioxidant, minimal novel fluid titrated) could be important. The HS studies are continuing in years 4 and 5 (2001-2003) under ONR support with Dr. Tisherman as P.I. and Dr. Safar as Co-P.I. In preparation for clinical trials, a trauma model in pigs has been added to our rat models.

Concerning CA (SA). Our dog data, so far without trauma, have clarified the limit of tolerance for up to 90 min (perhaps 120 min) CA no-flow at 10°C. This "first" should lead to clinical feasibility trials in trauma hospitals' emergency rooms, using rapid thoracotomy or femoral cutdown for access to the aorta, with pump and large volumes of cold fluid standby; and emergency (portable) CPB ready for resuscitation. Preservation of viability of brain and organism proved possible within the first 5 min of normothermic no flow. Taking SA into the out-of-hospital arena and the field for initiation by military medics will require a next phase of SA engineering (devices) research. **The main scientific significance of our SA results concerns the observation that pharmacologic preservation potentials pale in comparison to hypothermia.** After 20 years of frustrating drug-by-drug searches for cerebral resuscitation potentials, by us and others, our systematic exploration of many pharmacologic preservation potentials in the same model was a "first."

The clinical significance includes SA potentials for the many unresuscitable cases with normovolemic sudden cardiac death – to buy time for bridging to the initiation of prolonged CPB. This normovolemic CA study is planned for year 4. Relevance for that includes military casualties with CA without hemorrhage (e.g., chemical warfare). For all this we are coaching the development of devices and methods for rapid vessel access without thoracotomy (with smart catheters) (Dr. Klain, Dr. Yaffe; Cardeon Co.) and a miniaturized portable blood cooling/pumping device (Biocontrol Co.). With existing tools, a multicenter *clinical feasibility trial* in trauma centers' emergency departments, of mild Hth for traumatic HS, and of profound Hth for SA in exsanguination CA (flush via thoracotomy), feasible now, and is being planned now under the leadership of Dr. Tisherman. Subcontractor Dr. Champion helped clarify the number and types of suitable cases, using the National Trauma Database. ONR outcome research in rats and dogs should continue parallel with clinical trials. Continued animal work should pursue many still unanswered questions. These include how tissue injury and coagulopathy would influence our SA results so far without major tissue injury (relevant for exsanguination from a "simple" penetrating injury of a major vessel). For major tissue trauma, we just completed in year 4 the first SA study with major trauma. Military and civilian resuscitation potentials by paramedics vs physician teams, in field vs mobile ICU (or helicopter) vs field hospital, are merging since September 11, 2001. Capabilities and needs of special Armed Forces should make us re-think our research goals.

PATENT INFORMATION: No new patents since start of ONR funding. Earlier, the University of Pittsburgh, under Safar-Klain-Stezoski, obtained a patent for a portable multimodular cardiopulmonary bypass apparatus, and one for a single- or double-balloon aortic catheter. Both patents had been licensed to the Cardeon Corp. of California before start of this ONR project.

AWARD INFORMATION: See "other accomplishments," above.

PUBLICATIONS

Supported fully or in part by the Office of Naval Research (ONR) grants to the SCRR, University of Pittsburgh 1997-2001 (years 1, 2, and 3)

HEMORRHAGIC SHOCK (HS)

Refereed Publications on HS

1. Crippen, D., Safar, P., Porter, L., Zona, J. (1991) Improved survival of hemorrhagic shock with oxygen and hypothermia in rats. *Resuscitation* 21: 271-281. [*Background*, "first" for Hth in HS].
2. Capone, A., Safar, P., Stezoski, S.W., Peitzman, A., Tisherman, S. (1995) Uncontrolled hemorrhagic shock outcome model in rats. *Resuscitation* 29: 143-152. [*Background*].
3. Capone, A.C., Safar, P., Stezoski, W., Tisherman, S., Peitzman, A.B. (1995) Improved outcome with fluid restriction in treatment of uncontrolled hemorrhagic shock. *J Am Coll Surg* 180: 49-56. [*Background*].
4. Leonov, Y., Safar, P., Sterz, F., Stezoski, S.W. (2001) Extending the golden hour of hemorrhagic shock tolerance with oxygen plus hypothermia in awake rats. An exploratory study. *In press*, *Resuscitation* 2001.
5. Kim, S.H., Stezoski, S.W., Safar, P., Tisherman, S.A. (1998) Hypothermia, but not 100% oxygen breathing, prolongs survival time during *lethal* uncontrolled hemorrhagic shock in rats. *J Trauma* 44: 485-491. [*Background*].
6. Kim, S.H., Stezoski, S.W., Safar, P., Capone, A., Tisherman, S. (1997) Hypothermia and minimal fluid resuscitation increase *survival* after uncontrolled hemorrhagic shock in rats. *J Trauma* 42: 213-222. [*Background*].
7. Takasu, A., Carrillo, P., Stezoski, S.W., Safar, P., Tisherman, S. (1999) Mild or moderate hypothermia but not increased oxygen breathing prolong survival during *lethal* uncontrolled hemorrhagic shock in rats, with monitoring of visceral dysoxia. *Crit Care Med* 27: 1557-1564
8. Takasu, A., Stezoski, S.W., Stezoski, J., Safar, P., Tisherman, S.A. (2000) Mild or moderate hypothermia, but not increased oxygen breathing, increases long term *survival* after uncontrolled hemorrhagic shock in rats. *Crit Care Med* 28: 2465-2474.
9. Takasu, A., Prueckner, S., Tisherman, S.A., Stezoski, S.W., Stezoski, J., Safar, P. (2000) Effects of increased oxygen breathing in a volume controlled hemorrhagic shock outcome model in rats. *Resuscitation* 45: 209-220.
10. Prueckner, S., Safar, P., Kentner, R., Stezoski, J., Tisherman, S.A. (2001) Mild hypothermia increases survival from severe pressure controlled hemorrhagic shock in rats. *J Trauma* 50: 253-262.
11. Carrillo, P., Takasu, A., Safar, P., Tisherman, S., Stezoski, S.W., Stolz, G., Dixon, C.E., Radovsky, A. (1998) Prolonged severe hemorrhagic shock and resuscitation in rats does not cause subtle brain damage. *J Trauma* 45: 239-249.
12. Wu, X., Prueckner, S., Rollwagen, F., Kentner, R., Stezoski, J., Kochanek, P.M., Behringer, W., Pasculle, W.A., Safar, P., Tisherman, S.A. (2001) Gut damage during hemorrhagic shock: Effects on survival of oral or Enteral Interleukin-6. *Shock* 16: 449-453.
13. Barr, J., Prueckner, S., Safar, P., Tisherman, S.A., Radovsky, A., Stezoski, J., Eshel, G. (2000) Peritoneal ventilation with oxygen improves outcome after hemorrhagic shock in rats. *Crit Care Med* 28: 3896-3901.

14. Wu, X., Kentner, R., Stezoski, J., Kochanek, P.M., Jackson, E.K., Carlos, T.M., Carcillo, J., Behringer, W., Safar, P., Tisherman, S.A. (2001) Intraperitoneal, but not enteric, adenosine administration improves survival after volume-controlled hemorrhagic shock in rats. *Crit Care Med* 29: 1767-1773.
15. Kentner, R., Safar, P., Prueckner, S., Behringer, W., Wu, X., Henchir, J., Tisherman, S.A. (2002) Beneficial effects of titrated hypertonic/hyperoncotic solution during uncontrolled hemorrhagic shock in rats. *In preparation* for submission to *Resuscitation*.
16. Kentner, R., Safar, P., Behringer, W., Wu, X., Kagan, V.E., Tyurina, Y.Y., Henchir, J., Ma, L., Hsia, C.J.C., Tisherman, S.A. (2002) Early antioxidant therapy with Tempol during hemorrhagic shock increases survival in rats. *Submitted to, J Trauma* 2001.
17. Kentner, R., Rollwagen, F.M., Preuckner, S., Behringer, W., Wu, X., Stezoski, J., Safar, P., Tisherman, S.A. (2001). Effects of Mild Hypothermia on Survival and Serum Cytokines in Uncontrolled Hemorrhagic Shock in Rats. *Shock* (in press).
18. Wu, X., Kentner, R., Stezoski, J., Behringer, W., Safar, P., Tisherman, S.A. (2001) Systemic hypothermia, but not regional gut cooling, improves survival from prolonged hemorrhagic shock (HS) in rats. *Submitted to J Trauma*.
19. Wu, X., Stezoski, J., Safar, P., Kentner, R., Behringer, W., Kochanek, P., Tisherman, S.A. (2001) Delayed Mild Hypothermia prolongs survival following severe hemorrhagic shock (HS) in rats. *In preparation* for submission to *Crit Care Med*.
20. Wu, X., Kentner, R., Safar, P., Bauer, A., Tuerler, B., Behringer, W., Stezoski, J., Tisherman, S.A. (2001) Mild Hypothermia Improves Survival without Significant Effects on Inflammatory Responses in Rats. *In preparation* for submission to *Crit Care Med*.

Abstracts

21. Carrillo, P., Takasu, A., Tisherman, S., Stezoski, S.W., Stolz, G., Dixon, C.E., Radovsky, A., Safar, P. (1998) Does severe hemorrhagic shock (HS) cause subtle brain damage in rats? *J Trauma*. (Abstract). [EAST meeting 1998].
22. Takasu, A., Stezoski, S.W., Stezoski, J., Safar, P., Tisherman, S.A. (1998) Mild or moderate hypothermia, but not increased oxygen breathing, increases long-term survival after uncontrolled hemorrhagic shock in rats. *Acad Emerg Med* 5/5: 470. (Abstract) [SAEM Mtg. 1998].
23. Takasu, A., Carrillo, P., Stezoski, S.W., Safar, P., Tisherman, S.A. (1998) Both mild (34°C) and moderate (30°C) hypothermia (Hth), but not 100% O₂ breathing, prolonged survival time during *lethal* uncontrolled hemorrhagic shock. *Crit Care Med* 26: A48. (Abstract). [SCCM meeting 1998].
24. Takasu, A., Prueckner, S., Safar, P., Stezoski, S.W., Stezoski, J., Tisherman, S.A. (1999) Effects of increased oxygen breathing in a volume-controlled hemorrhagic shock (HS) outcome model in rats. *Crit Care Med* 27/1: A177. (Abstract #493). [SCCM meeting 1999].
25. Prueckner, S., Kagan, V.E., Tyurina, Y.Y., Safar, P., Tisherman, S.A., Stezoski, J., Stezoski, S.W. (1999) Reduction of overall antioxidant reserve in liver and small intestine after uncontrolled hemorrhagic shock and resuscitation in rats. *Crit Care Med* 27/1: A106. (Abstract #233). [SCCM meeting 1999].
26. Barr, J., Prueckner, S., Safar, P., Tisherman, S.A., Stezoski, J. (1999) Does peritoneal ventilation with 100% oxygen (PV-O₂) during and after severe hemorrhagic shock (HS) protect viscera and improve outcome? A preliminary study in rats. *Crit Care Med* 27/1: A136. (Abstract #340). [SCCM meeting 1999].

27. Prueckner, S., Tisherman, S.A., Stezoski, J., Stezoski, S.W., Safar, P. (1999) Intestinal dysoxia monitoring in uncontrolled hemorrhagic shock (HS) and resuscitation in rats: Intraluminal vs serosal PCO₂. *Anesthesiology* 91: A241. (Abstract). [ASA meeting 1999].
28. Prueckner, S., Rollwagen, F., Tisherman, S., Stezoski, J., Safar, P. (1999) Apoptosis and necrosis in liver and small intestine early after uncontrolled hemorrhagic shock (HS) and resuscitation in rats. *Anesthesiology* 91: A240. (Abstract). [ASA meeting 1999].
29. Prueckner, S., Safar, P., Kentner, R., Stezoski, J., Tisherman, S.A. (1999) Mild hypothermia increases survival from severe pressure controlled hemorrhagic shock in rats. *J Trauma* 47: 1172 (Abstract). [EAST meeting 2000].
30. Tisherman, S., Wu, X., Prueckner, S., Rollwagen, F.M., Stezoski, J., Safar, P. (2000) Enteral or oral IL-6 does not improve survival in rats during hemorrhagic shock. *Shock* 13 (suppl): 48. (Abstract). [Shock meeting 2000].
31. Wu, X., Jackson, E.K., Stezoski, J., Tisherman, S., Safar, P. (2000) Intraperitoneal (IP) but not enteric (EN) adenosine improves survival after prolonged volume-controlled hemorrhagic shock (HS) in rats. *Shock* 13 (suppl): 49. (Abstract). [Shock meeting 2000].
32. Safar, P., Kentner, R., Prueckner, S., Behringer, W., Wu, X., Tisherman, S.A. (2000) Titrated hypertonic/hyperoncotic solution (HHS) reduces infusion volume requirement during uncontrolled hemorrhagic shock (UHS) in rats. *Shock* 13 (suppl): 47. (Abstract). [Shock meeting 2000].
33. Kentner, R., Khan, L., Tisherman, S., Rollwagen, F., Safar, P. (2000) Effects of mild hypothermia on serum cytokines and outcome in uncontrolled hemorrhagic shock (UHS) in rats. *Shock* 13 (suppl): 43. (Abstract). [Shock meeting 2000].
34. Kentner, R., Prueckner, S., Behringer, W., Wu, X., Henchir, J., Safar, P., Tisherman, S.A. (2000) Titrated hypertonic/hyperoncotic solution (HHS) does not increase blood loss during uncontrolled hemorrhagic shock (UHS) in rats. *Trauma Care* 10/1: 38. (Abstract). [ITACCS meeting 2000].
35. Kentner, R., Tisherman, S.A., Rollwagen, F., Behringer, W., Safar, P. (2000) Effects of mild hypothermia on cytokine response and outcome after uncontrolled hemorrhagic shock (UHS) in rats. *Trauma Care* 10/1: 39. (Abstract). [ITACCS meeting 2000]. Ms submitted to Shock.
36. Kentner, R., Wu, X., Behringer, W., Henchir, J., Tisherman, S.A., Ma, L., Hsia, C.J.C., Safar, P. (2000) Effects of polynitroxylated albumin (PNA) plus tempol during and after hemorrhagic shock (HS) in rats. *Trauma Care* 10/1: 39. (Abstract). [ITACCS meeting 2000].
37. Kentner, R., Safar, P., Hsia, C.J.C., Kagan, V., Tisherman, S.A. (2000) Antioxidant polynitroxylated albumin (PNA) plus tempol for hemorrhagic shock (HS) in rats I: Effects of late treatment. *Anesthesiology* 93 (Suppl): A485. (Abstract). [ASA meeting 2000].
38. Kentner, R., Safar, P., Behringer, W., Hsia, C.J.C., Tisherman, S.A. (2000) Antioxidant polynitroxylated albumin (PNA) plus Tempol for hemorrhagic shock (HS) in rats II: Improved survival with early treatment. *Anesthesiology* 93 (Suppl): A484. (Abstract). [ASA meeting 2000].
39. Wu, X., Safar, P., Jackson, E., Carcillo, J., Tisherman, S.A. (2000) Effects of intraperitoneal (IP) and enteric (EN) adenosine on survival and circulating cytokines and after prolonged volume-controlled hemorrhagic shock (HS) in rats. *Anesthesiology* 93 (Suppl): A500. (Abstract). [ASA meeting 2000].
40. Kentner, R., Safar, P., Behringer, W., Wu, X., Kagan, V., Rollwagen, F., Hsia, C.J.C., Tisherman, S.A. (2000) Antioxidant polynitroxylated albumin (PNA) plus tempol is protective during and after hemorrhagic shock (HS) in rats. (Abstract). [Presented at New York Postgraduate Assembly of Anesthesiologists 2000].

41. Kentner, R., Safar, P., Prueckner, S., Behringer, W., Stezoski, J., Tisherman, S.A. (1999) Uncontrolled hemorrhagic shock (UHS) in rats, I: Ringer's solution vs blood and mild hypothermia. *Crit Care Med* 27/12: A156. (Abstract #447). [SCCM meeting 2000].
42. Kentner, R., Safar, P., Prueckner, S., Henchir, J., Tisherman, S.A. (1999) Uncontrolled hemorrhagic shock (UHS) in rats, II: Development of a new outcome model. *Crit Care Med* 27/12: A154. (Abstract #440). [SCCM meeting 2000].
43. Wu, X., Kentner, R., Stezoski, J., Behringer, W., Safar, P., Tisherman, S.A. (2001) Systemic hypothermia, but not regional gut cooling, improves survival from prolonged hemorrhagic shock (HS) in rats. *In press, J Trauma*. (Abstract). [American Association for the Surgery of Trauma mtg. 2001].
44. Wu, X., Kentner, R., Safar, P., Bauer, A., Tuerler, A., Behringer, W., Stezoski, J., Tisherman, S. (2000) Mild hypothermia during hemorrhagic shock (HS) improves survival without significant effects on inflammatory responses in rats. *Crit Care Med* 28/12: A139. (Abstract #396). [SCCM meeting 2001].
45. Kentner, R., Wu, X., Safar, P., Henchir, J., Hsia, C. (2001) Doubling the "golden hour" of traumatic hemorrhagic shock tolerance with mild hypothermia and an anti-oxidant. *Proceedings of American Society of Anesthesiologists, New Orleans, October 2001*. Abstract #388, page 214. [ASA meeting.2001].
46. Wu, X., Safar, P., Stezoski, J., Kentner, R., Behringer, W., Tisherman, S.A. (2001) Delayed mild hypothermia prolonged survival following severe hemorrhagic shock (HS) in rats. *Shock* 15: 49. (Abstract 146). [Shock meeting 2001].
47. Wu, X., Fink, M., Stezoski, J., Safar, P., Behringer, W., Tisherman, S.A. (2002) Resuscitation with Ringer's ethyl pyruvate solution (REPS) fails to improve long term survival compared to lactated Ringer's (LR) solution after severe volume-controlled hemorrhagic shock (HS) in rats. *In press, Crit Care Med*. (Abstract). [SCCM meeting 2002].
48. Wu, X., Clay, C., Stezoski, J., Behringer, W., Safar, P., Tisherman, S.A. (2002) Inhibition of sodium/hydrogen ion (Na⁺/H⁺) exchange with methyl isobutyl amiloride impairs tolerance to hemorrhagic shock in rats. *In press, Crit Care Med*. (Abstract). [SCCM meeting 2002].
49. Wu, X., Safar, P., Subramanian, M., Behringer, W., Tisherman, S.A. (2002) Mild hypothermia (34°C) does not increase initial bleeding from the injured liver after hemorrhagic shock (HS) in pigs. *In press, Crit Care Med*. (Abstract). [SCCM meeting 2002].

SUSPENDED ANIMATION (SA)

Refereed Publications on (SA)

50. Tisherman, S.A., Safar, P., Radovsky, A., Peitzman, A., Marrone, G., Kuboyama, K., Weinrauch, V. (1991) Profound hypothermia (<10°C) compared with deep hypothermia (15°C) improves neurologic outcome in dogs after two hours' circulatory arrest induced to enable resuscitative surgery. *J Trauma* 31: 1051-1062. [Background]
51. Capone, A., Safar, P., Radovsky, A., Wang, Y., Peitzman, A., Tisherman, S.A. (1996) Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. *J Trauma* 40:388-394. [Background]

52. Bellamy, R., Safar, P., Tisherman, S.A., Basford, R., Bruttig, S.P., Capone, A., Dubick, M.A., Ernster, L., Hattler, B.G. Jr., Hochachka, P., Klain, M., Kochanek, P.M., Kofke, W.A., Lancaster, J.R., McGowan, F.X., Oeltgen, P.R., Severinghaus, J.W., Taylor, M.J., Zar, H. (1996) Suspended animation for delayed resuscitation. *Crit Care Med* 24/S: S24-47. [*Background*]
53. Woods, R.J., Prueckner, S., Safar, P., Radovsky, A., Takasu, A., Stezoski, S.W., Stezoski, J., Tisherman, S.A. (1999) Hypothermic aortic arch flush for preservation during exsanguination cardiac arrest of 15 minutes in dogs. *J Trauma* 47: 1028-1038.
54. Behringer, W., Prueckner, S., Safar, P., Radovsky, A., Kentner, R., Stezoski, S.W., Henchir J., Tisherman, S.A. (2000) Rapid induction of mild cerebral hypothermia by cold aortic flush achieves normal recovery in a dog outcome model with 20-minute exsanguination cardiac arrest. *Acad Emerg Med* 7: 1341-1348.
55. Woods, R.J., Prueckner, S., Safar, P., Takasu, A., Tisherman, S.A., Jackson, E.K., Radovsky, A., Kochanek, P., Behringer, W., Stezoski, S.W., Hans, R. (2000) Adenosine by aortic flush fails to augment the brain preservation effect of mild hypothermia during exsanguination cardiac arrest in dogs. An exploratory study. *Resuscitation* 44: 47-59.
56. Behringer, W., Kentner, R., Wu, X., Tisherman, S.A., Radovsky, A., Stezoski, W.S., Henchir, J., Prueckner, S., Safar, P. (2001) Thiopental and phenytoin by aortic arch flush for cerebral preservation during exsanguination cardiac arrest of 20 minutes in dogs. An exploratory study. *Resuscitation* 49: 83-97.
57. Behringer, W., Kentner, R., Wu, X., Tisherman, S.A., Radovsky, A., Stezoski, W.S., Henchir, J., Prueckner, S., Jackson, E.K., Safar, P. (2001) Fructose-1,6-bisphosphate and MK-801 by aortic arch flush for cerebral preservation during exsanguination cardiac arrest of 20 minutes in dogs. An exploratory study. *Resuscitation* 50: 205-216.
58. Behringer, W., Safar, P., Kentner, R., Wu, X., Kagan, V.E., Radovsky, A., Clark, R.S.B., Kochanek, P.M., Subramanian, M., Tyurin, V.A., Tyurina, Y., Tisherman, S.A. (2001) Antioxidant Tempol enhances hypothermic cerebral preservation during prolonged cardiac arrest in dogs. *In press, J Cerebr Blood Flow Metab* 2001.
59. Behringer, W., Safar, P., Wu, X., Kentner, R., Prueckner, S., Radovsky, A., Kochanek, P.M., Jackson, E.K., Jenkins, L.W., Tisherman, S.A. (2001) Disappointing cerebral preservation with drugs during prolonged cardiac arrest. Systematic exploration of fourteen drugs in dogs. *Submitted, rejected, being revised for other journal* (1-2002).
60. Behringer, W., Prueckner, S., Kentner, R., Tisherman, S.A., Radovsky, A., Clark, R., Stezoski, S.W., Henchir, J., Klein, E., Safar, P. (2000) Rapid hypothermic aortic flush can achieve survival without brain damage after 30 minutes cardiac arrest in dogs. *Anesthesiology* 93: 1491-1499.
61. Behringer, W., Safar, P., Wu, X., Kentner, R., Radovsky, A., Kochanek, P.M., Dixon, C.E., Tisherman, S.A. (2001) Survival without brain damage after suspended animation for 1-2 hours of cardiac arrest in dogs. *Submitted to JAMA, rejected, being revised for Crit Care Med*.
62. Behringer, W., Safar, P., Nozari, A., Wu, X., Kentner, R., Tisherman, S.A., Radovsky, A. (2002) Intact survival of 120 min cardiac arrest at 10°C in dogs. Cerebral preservation by cold aortic flush with optimized solutions. *In preparation*.
63. Safar, P., Tisherman, S.A., Behringer, W., Capone, A., Prueckner, S., Radovsky, A., Stezoski, S.W., Woods, R.J. (2000) Suspended animation for delayed resuscitation from prolonged cardiac arrest that is unresuscitable by standard cardiopulmonary-cerebral resuscitation. *Crit Care Med* 28 (Suppl): N214-N218. [Wolf Creek V meeting 6/99].

64. Safar, P., Behringer, W., Boettiger, B.W., Sterz, F. (2001) Cerebral resuscitation potentials for cardiac arrest. *In press*, Crit Care Med, (Suppl); 2001. [Wolf Creek VI meeting 6/01].

Abstracts on SA

65. Prueckner, S., Woods, R.J., Safar, P., Takasu, A., Stezoski, S.W., Radovsky, A., Tisherman, S.A. (1999) Mild hypothermic aortic arch flush improves neurologic outcome from exsanguination cardiac arrest in dogs. Crit Care Med 27/1: A105. (Abstract #227). [SCCM meeting 1999].
66. Woods, R.J., Prueckner, S., Safar, P., Takasu, A., Tisherman, S.A., Jackson, E.K., Radovsky, A., Kochanek, P., Stezoski, S.W., Stezoski, J. (1999) *Adenosine* by aortic flush fails to augment the brain preservation effect of mild hypothermia during exsanguination cardiac arrest in dogs. Crit Care Med 27/1: A106. (Abstract #231). [SCCM meeting 1999].
67. Behringer, W., Prueckner, S., Tisherman, S.A., Radovsky, A., Safar, P. (1999) Cold aortic flush for rapid induction of cerebral preservation during exsanguination cardiac arrest (ExCA) of 30 min in dogs. Anesthesiology 91: A250. (Abstract). [ASA meeting 1999].
68. Behringer, W., Prueckner, S., Tisherman, S.A., Radovsky, A., Safar, P. (1999) *Thiopental* (TH) by aortic flush (AAF) for cerebral preservation in a 20-min exsanguination cardiac arrest (CA) exploratory dog study. Anesthesiology 91: A251. (Abstract). [ASA meeting 1999].
69. Prueckner, S., Clark R, Woods, R.J., Behringer, W., Khan, L., Radovsky, A., Stezoski, W., Safar, P., Tisherman, S.A. (1999) Cold aortic arch flush decreases apoptosis after exsanguination cardiac arrest in dogs. Crit Care Med 27/12: A30. (Abstract #30). [SCCM meeting 2000].
70. Behringer, W., Prueckner, S., Kentner, R., Safar, P., Radovsky, A., Stezoski, W., Henchir, J., Tisherman, S.A. (1999) Combination treatment of phenytoin and thiopental by aortic arch flush for cerebral preservation during 20 min exsanguination cardiac arrest (ExCA) in dogs. Exploratory experiments. Crit Care Med 27/12: A29. (Abstract #27). [SCCM meeting 2000].
71. Behringer, W., Prueckner, S., Kentner, R., Safar, P., Radovsky, A., Stezoski, W., Wu, X., Henchir, J., Tisherman, S.A. (1999) Exploration of pharmacologic aortic arch flush strategies for rapid induction of suspended animation (SA) (cerebral preservation) during exsanguination cardiac arrest (ExCA) of 20 min in dogs. Crit Care Med 27/12: A65. (Abstract #151). [SCCM meeting 2000]. [Submitted].
72. Behringer, W., Prueckner, S., Radovsky, A., Tisherman, S.A., Safar, P. (2000) Suspended animation (SA) I: Hypothermic aortic flush during prolonged exsanguination cardiac arrest (ExCA) in dogs. Anesthesiology 93 (Suppl): A473. (Abstract). [ASA meeting 2000].
73. Behringer, W., Kentner, R., Radovsky, A., Tisherman, S.A., Safar, P. (2000) Suspended animation (SA) II: Pharmacologic aortic flush during prolonged exsanguination cardiac arrest (ExCA) in dogs. Anesthesiology 93 (Suppl): A474. (Abstract). [ASA meeting 2000].
74. Behringer, W., Wu, X., Radovsky, A., Tisherman, S.A., Safar, P. (2000) Tempol by aortic arch flush (AAF) for cerebral preservation during 20 min exsanguination cardiac arrest (CA) in dogs. Exploratory experiments. Anesthesiology 93 (Suppl): A475. (Abstract). [ASA meeting 2000].
75. Wu, X., Behringer, W., Kentner, R., Tisherman, S.A., Safar, P. (2000) Liver damage during prolonged cardiac arrest (CA) in dogs. Anesthesiology 93 (Suppl): A501. (Abstract). [ASA meeting 2000].
76. Behringer, W., Safar, P., Prueckner, S., Kentner, R., Wu, X., Woods, R., Radovsky, A., Clark, R., Stezoski, W., Tisherman, S.A. (2000) Suspended animation (SA) I: Hypothermic aortic flush during prolonged exsanguination cardiac arrest (ExCA) in dogs. (Abstract). [European Resuscitation Council meeting, Antwerp, June 2000].

77. Behringer, W., Safar, P., Prueckner, S., Kentner, R., Wu, X., Woods, R., Radovsky, A., Kochanek, P., Jackson, E., Tisherman, S.A. (2000) Suspended animation (SA) II: Pharmacologic aortic flush during prolonged exsanguination cardiac arrest (ExCA) in dogs. (Abstract). [European Resuscitation Council meeting, Antwerp, June 2000].
78. Safar, P., Behringer, W., Tisherman, S. (2000) Suspended animation (SA) III: Preservation potentials for delayed resuscitation from "unresuscitable" normovolemic cardiac arrest (CA). (Abstract). [European Resuscitation Council meeting, Antwerp, June 2000].
79. Behringer, W., Safar, P., Kentner, R., Wu, X., Stezoski, W.S., Radovsky, A., Sakai, Y., Tisherman, S.A. (2000) Intact survival of 60, 90, and 120 min cardiac arrest in dogs with 10°C cerebral preservation by cold aortic flush. Study II. *Crit Care Med* 28/12: A65. (Abstract #128). [SCCM meeting 2001].
80. Behringer, W., Safar, P., Kentner, R., Wu, X., Stezoski, W.S., Radovsky, A., Sakai, Y., Tisherman, S.A. (2000) Survival of 60 min cardiac arrest in dogs with 15°C vs 20°C cerebral preservation by cold aortic flush. Study I. *Crit Care Med* 28/12: A67. (Abstract #134). [SCCM meeting 2001].
81. Behringer, W., Safar, P., Wu, X., Kentner, R., Kagan, V., Radovsky, A., Stezoski, W.S., Henschir, J., Tisherman, S.A. (2000) Antioxidant Tempol enhances hypothermic cerebral preservation during 40 min cardiac arrest in dogs. *Crit Care Med* 28/12: A67. (Abstract #135). [SCCM meeting 2001].
82. Behringer, W., Safar, P., Nozari, A., Wu, X., Kentner, R., Tisherman, S.A., Radovsky, A. (2002) Intact survival of 120 min cardiac arrest at 10°C in dogs. Cerebral preservation by cold aortic flush. *In press, Crit Care Med.* (Abstract). [SCCM meeting 2002].
83. Behringer, W., Safar, P., Kentner, R., Wu, X., Radovsky, A., Tisherman, S.A., Taylor, M., Hsia, C. (2002) Novel solutions for intra-ischemic aortic cold flush for preservation during 30 min cardiac arrest in dogs. *In press, Crit Care Med.* (Abstract). [SCCM meeting 2002].
84. Behringer, W., Safar, P., Wu, X., Kentner, R., Radovsky, A., Tisherman, S.A. (2002) Delayed intra-ischemic aortic cold flush for preservation during prolonged cardiac arrest in dogs. *In press, Crit Care Med.* (Abstract). [SCCM meeting 2002].
85. Behringer, W., Safar, P., Wu, X., Nozari, A., Abdulah, A., Tisherman, S.A. (2002) Veno-venous extracorporeal blood cooling for rapid induction of mild hypothermia in dogs. *In press, Crit Care Med.* (Abstract). [SCCM meeting 2002].
86. Khan, L., Prueckner, S., Behringer, W., Rajendiran, S., Klein, E.C., Kentner, R., Tisherman, S.A., Safar, P. (2000) Extracerebral postresuscitation disease after cardiac arrest (CA) in dogs. A preliminary report. *Crit Care Med* 27/12: A67. (Abstract). [SCCM meeting 2000].
87. Behringer, W., Safar, P. (2001) Potentials and limits of hypothermic vs. pharmacologic cerebral preservation-resuscitation for prolonged cardiac arrest (CA) in dogs. (Abstract). [Wolf Creek VI meeting 6/01]

Miscellaneous (books, o.e.) by authors when partially supported by ONR

- M1. SCRR Annual Reports 1998/1999, 1999/2000, 2000/2001 (in preparation) available from SCRR Director, Patrick Kochanek.
- M2. Safar, P., Behringer, W. (2001) Cerebral resuscitation from cardiac arrest. *Chapter in, A Textbook of NeuroIntensive Care.* Layon AJ, Gabrielli A, Friedman WA (editors). WB Saunders Publ. *In press*, Sept. 2001.

- M3. Safar, P., Kochanek, P.M. (1999) Resuscitating and protecting the brain. Chapter in Oxford Textbook of Critical Care. Webb, A., et al (eds), Oxford University Press, New York, pp 18-20.
- M4. Tisherman, S.A., Rodriguez, A., Safar, P. (1999) Therapeutic hypothermia in traumatology. Chapter in Surgery Clinics of North America 79: 1269-1289.
- M5. Tisherman, S.A. (1998) Hypothermia, cold, injury, and drowning. In: Peitzman, A.B., Rhodes, M., Schwab, C.W., Yealy, D., eds. The Trauma Manual, Lippincott-Raven, pp 394-400. [Chapter].
- M6. Rubertsson, S., Safar P. (1998) Cardiopulmonary-cerebral resuscitation. In, Grenvik A (ed), Textbook of CCM. W.B. Saunders Co., Philadelphia, pp 9-20. Chapter 1.
- M7. Safar, P. (2001) "Cerebral resuscitation from temporary complete global brain ischemia." Invited keynote lecture presented at the Fifth Annual Symposium on Applied Physiology of the Peripheral Circulation. Cerebral blood flow: Mechanisms of ischemia, diagnosis and therapy. June 9, 2000, Pittsburgh. Chapter. Springer Verlag *in press*.
- M8. Eisenburger, P., Safar, P. (1999) Life supporting first aid (LSFA) training of the public. Review and Recommendations. Resuscitation 41 :3-18.
- M9. Kochanek, P.M., Uhl, M.W., Schoettle, R.J., Katz, L., Clark, R.S.B., Safar, P. (1998) Hypoxic-ischemic encephalopathy. Biology and therapy of the postresuscitation syndrome in children. In: Pediatric Critical Care. Fuhrman, Zimmerman (eds), Mosby Publishers, St. Louis, MO, 671-691. Chapter 58.
- M10. Safar, P. (2000) From Vienna to Pittsburgh for anesthesiology and acute medicine. Careers in Anesthesiology. Invited Autobiographical Memoirs. American Society of Anesthesiologists, Wood Library-Museum. (Wood Library Museum, 515 Busse Highway, Park Ridge, IL 60068). [370 pg. book].
- M11. Safar, P. (2001) On the history of emergency medical services. Bulletin of Anesthesia History, vol. 19, 2001. [Chapter].
- M12. Safar, P. (2001) Development of cardiopulmonary-cerebral resuscitation in the twentieth century. Fifth International Symposium on the History of Anesthesia. Santiago de Compostela, Spain, September 20, 2001. [Chapter].
- M13. Safar, P. (2001) From control of airway and breathing to cardiopulmonary-cerebral resuscitation. Anesthesiology 95: 789-791. [First in a new invited series of *Classic Papers revisited*].
- M14. Safar, P. (2000) "On the future of Reanimatology." Keynote lecture at the Society for Academic Emergency Medicine (SAEM) Meeting, Boston, 1999. Acad Emerg Med 7: 75-89.
- M15. Safar, P. (2001) The Resuscitation Greats. Vladimir A. Negovsky the father of 'reanimatology.' Resuscitation 49: 223-229.
- M16. Safar, P. (2001) The Resuscitation Greats. James O. Elam, MD, 1918-1995. Resuscitation 50: 249-256.
- M17. Ebmeyer, U., Safar, P., Radovsky, A., Obrist, W., Alexander, H., Pomeranz, S. (1998): Moderate hypothermia for 48 hours after temporary epidural brain compression injury in a canine outcome model. J Neurotrauma 15:323-336.
- M18. Ebmeyer, U., Safar, P., Radovsky, A., Xiao, F., Capone, A., Tanigawa, K., Stezoski, S.W. (2000) Thiopental combination treatments for cerebral resuscitation after prolonged cardiac arrest in dogs. Exploratory outcome study. Resuscitation 45: 119-131.

- M19. Ebmeyer, U., Safar, P., Radovsky, A., Sharma, C., Xiao, F., Tanigawa, K., Wang, Y., Stezoski, S.W. (2001) Increasing cerebral oxygen delivery after prolonged cardiac arrest in dogs. An exploratory outcome study. *In preparation for Resuscitation*.
- M20. Eshel, G.M., Safar, P., Sassano, J., Stezoski, S.W. (1998) Delayed death after uncomplicated hot tub bathing in dogs and monkeys. *Resuscitation* 37:189-195.
- M21. Safar, P., Bircher, N., Pretto, E., Berkebile, P., Tisherman, S.A., Marion, D., Klain, M., Kochanek, P.M. (1998) Reappraisal of mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation. (Letters to Editors). *Resuscitation* 36:75-80; *Ann Emerg Med* 31:653-655; *Circulation* 98:608-609; *Respir Care* 43:122-127.
- M22. Safar, P. (1999) Ventilation and cardiopulmonary resuscitation. *Current Opinion in Anaesthesiology* 12: 165-171.
- M23. Safar, P.J., Kochanek, P.M. (2002) Resuscitative hypothermia after cardiac arrest. Invited editorial comment on Bernard, et al, and Holzer, et al, *N Engl J Med*, *in press*, Jan. 2002.*
- M24. Safar, P., Kochanek, P., Bircher, N. (2000) Editorial comment on Hallstrom, et al. Cardiopulmonary resuscitation by chest compression alone, *NEJM* 342: 1546. *New Engl J Med* 343: 816-817.
- M25. Safar, P., Kochanek, P.M. (2001) Editorial comment on Clifton, et al. Lack of effect of induction of hypothermia after acute brain injury, *NEJM* 344: 556. *N Engl J Med* 345: 66.
- M26. Safar, P. (2001) Editorial comment on Eisenberg, et al. Cardiac resuscitation, *NEJM* 344: 1304. *N Engl J Med* 345: 546.
- M27. Safar, P., Kochanek, P. (2000) Cerebral blood flow promotion after prolonged cardiac arrest. Editorial. *Crit Care Med* 28: 3104-3106. [Invited editorial].
- M28. Sasser, H.C., Safar, P., Kelsey, S.F., Ricci, E.M., Sutton-Tyrrell, K.C., Wisniewski, S.R. (1999) Arterial hypertension after cardiac arrest is associated with good cerebral outcome in patients. *Crit Care Med* 27/12: A29. (Abstract #28). [SCCM meeting 2000]. Ms. in preparation for JAMA.
- M29. Sasser, H.C., Safar, P., BRCT Study Group. (1999) Clinical signs early after CPR predict neurologic outcome. *Crit Care Med* 27/12: A30 (Abstract #29). [SCCM meeting 2000]. Ms. submitted to Lancet.
- M30. Safar, P. (2000) Resuscitation Medicine from 1000 to 2000 C.E. Lewis H. Wright Memorial Lecture presented at the ASA Annual Meeting, October 17, 2000, San Francisco, CA. ASA Annual Meeting News (abstract). Video tape available through ASA Wood Library Museum.
- M31. Safar, P. (2000, 2001). Resuscitative hypothermia for cardiac arrest. (Synopsis) Proceedings of Cleveland Clinic in December 2000 and September 2001.
- M32. Safar, P. (1998) Future potentials in reanimatology. Keynote lecture, abstract for Pan-American Congress of Disaster and Emergency Medicine, March 1998, San Jose, Costa Rica, proceedings.
- M33. Safar, P. (1998) Resuscitation for trauma during the 20th century. Keynote lecture for International Trauma Anesthesia and Critical Care Society Symposium, May 1998, Vienna, proceedings. [Abstract].
- M34. Behringer, W., Safar, P., Wu, X., Nozari, A., Abdullah, A., Stezoski, S.W., Tisherman, S.A. (2001) Veno-venous extracorporeal blood shunt cooling to induce mild hypothermia in dogs. Experiments and review of cooling methods. *Submitted, Resuscitation* 2001.